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REVIEW ARTICLE

PLATELETS IN INFLAMMATORY DISEASES: MEDIATORS OF CLOTTING AND IMMUNE RESPONSES

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ABSTRACT: Excessive and uncontrolled inflammation, coupled with thrombosis, are defining features of immune-mediated inflammatory disorders (IMIDs), contributing to organ damage, increased morbidity, and mortality. While platelets are primarily known for their role in clot formation, emerging research highlights their significant influence on inflammation and immune responses. Platelets engage with white blood cells and accumulate at injury sites, releasing cytokines and chemokines that attract neutrophils and monocytes, thereby amplifying the inflammatory response. In IMID patients, platelets are often activated by disease-specific triggers, with their activation levels correlating closely with disease activity. Beyond clotting, platelets exhibit immune cell-like behavior by engulfing pathogens, contributing to innate immunity. They also play a pivotal role in abnormal tissue healing and injury. Additionally, platelet-derived extracellular vesicles, laden with bioactive molecules, exacerbate inflammation, modulate immune responses, and promote thrombosis, thereby influencing disease progression. In autoimmune diseases, platelets not only support clotting and inflammation but also intensify autoimmunity by activating immune cells and perpetuating inflammatory feedback loops. Research into therapies targeting platelet activation and platelet-immune cell interactions presents promising strategies for managing IMIDs and reducing associated organ damage.

Keywords: - Intermediated seditious conditions (IMIDs), Platelets, Immune system

INTRODUCTION:

Platelets, small, disc-shaped anucleate cells derived from megakaryocytes, are best known for their essential role in hemostasis. However, emerging evidence underscores their multifaceted involvement in infection, inflammation, immune modulation, and even cancer progression. Beyond clot formation, platelets express and release adhesion molecules upon injury, facilitating their accumulation at the site of tissue damage [1].

These molecules not only mediate platelet adhesion to granulocytes and leukocytes but also contribute to the recruitment of immune cells. By secreting chemokines, platelets attract neutrophils, monocytes, and lymphocytes, leading to the formation of platelet-leukocyte or platelet-granulocyte aggregates that amplify inflammatory responses [2, 3].

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Importantly, the role of platelets extends to innate immunity, where they capture and engulf microorganisms, restricting bacterial dissemination through clot formation [4]. Their interactions with immune cells and modulation of inflammatory pathways are increasingly recognized as critical factors in the pathogenesis of immune-mediated inflammatory disorders (IMIDs). For instance, platelet-driven recruitment and activation of leukocytes may exacerbate chronic inflammation observed in conditions such as systemic lupus erythematosus, rheumatoid arthritis, and inflammatory bowel disease. Understanding these mechanisms offers potential therapeutic insights, positioning platelets as both biomarkers and targets in IMIDs.

Each microliter of blood typically contains 150,000 to 400,000 platelets, which are small cellular fragments derived from megakaryocytes. Platelets contain three distinct types of granules:

1. **Alpha Granules:**
   - Store coagulation factors, platelet-derived growth factors (PDGF), and transforming growth factor-beta (TGF-β).
   - Contain chemokines such as CXCL7, CXCL4, CXCL1, CXCL5, CCL5, and CCL3.
   - Other components include P-selectin, fibrinogen, von Willebrand factor (vWF), and fibronectin.
2. **Dense Granules:**
   - Rich in serotonin, which plays a significant role in promoting neutrophil recruitment during acute inflammation.
3. **Lysosomal Granules:**
   - Contain proteases such as cathepsins, acid phosphatase, collagenase, elastase, and glycohydrolases [5] [6,7].

Platelets release adhesion molecules like P-selectin, which are crucial for thrombus formation. P-selectin binds to PSGL-1 on cells, promoting the production of superoxide anions, neutrophil rolling, and transendothelial migration. These processes contribute to increased cardiovascular risk in immune-mediated inflammatory diseases (IMIDs) and exacerbate end-organ damage. Furthermore, TLR7 agonists enhance P-selectin expression, intensifying platelet-leukocyte interactions. Platelets also express β1, β2, and β3 integrins, facilitating their adhesion to the extracellular matrix and fibrinogen [8,9].

Megakaryocytes produce and store chemokines like RANTES in platelet granules. Upon release, RANTES enhances CD8 T-cell cytotoxicity and cytokine production while attracting additional monocytes from circulation. Platelet factor 4 has demonstrated anti-parasitic properties by killing intra-erythrocytic parasites. Additionally, platelets store thrombocidin, a chemokine-derived peptide with antibacterial and antifungal properties, highlighting their vital role in innate immunity [10,11].

MECHANISM OF PLATELET ACTIVATION

Platelet Activation and Its Role in Autoimmune and Inflammatory Diseases

Mechanisms of Platelet Activation

Platelets, which continuously circulate in the bloodstream, undergo a multifaceted activation process triggered by various stimuli. Key mechanisms of activation include:

1. **Morphological Transformation:** Platelets shift into a spherical shape while forming lamellipodia, a process driven by calcium release that activates the actin-myosin cytoskeleton.
2. **Externalization of Phospholipids and Granule Release:** Activation leads to the externalization of negatively charged phospholipids and the release of granules (dense and α-granules) containing molecules such as P-selectin and CD40L.
3. **Extracellular Vesicle Formation:** Platelets release extracellular vesicles, enabling the transport of platelet-derived molecules to areas beyond their direct reach.
4. **Biochemical Triggers in Autoimmune Diseases:** Autoimmune conditions like systemic lupus

erythematosus (SLE) and psoriasis stimulate platelet activation through signals such as ATP, a damage-associated molecular pattern (DAMP), and enzymes like ectonucleosidases CD39 and CD73. Impaired CD73 activity in these conditions disrupts the ATP-adenosine equilibrium.

5. **Physical Stimuli:** Physical triggers such as Raynaud's phenomenon, characterized by painful ischemia and vasoconstriction, also activate platelets.

These triggers initiate distinct signaling pathways, which can act synergistically to amplify platelet activation, leading to diverse platelet phenotypes [4, 5, 10–12] [12, 13].

Impact of Platelet Activation

Immune-Mediated Inflammatory Diseases

Research highlights the role of platelet activation in conditions such as rheumatoid arthritis, where activated platelets migrate to inflamed joints and circulate through the lymphatic system [13].

Antigen Presentation

Activated platelets express MHC class I molecules, primarily absorbed from plasma, which translocate to the platelet surface to interact with T cells. This process, facilitated by CD86, establishes a synapse between platelets and T cells. Additionally, extracellular vesicles released by platelets contribute to antigen processing and presentation. Megakaryocytes can also act as antigen-presenting cells, using MHC class I molecules and promoting CD4+ T cell activation and proliferation through MHC class II expression [14].

Interactions with Endothelial Cells

Activated platelets engage endothelial cells, promoting immunothrombosis and strengthening local immune defenses against pathogens. Platelet-derived IL-1β increases endothelial permeability, supporting tissue repair and immune responses. Interactions between platelet P-selectin and endothelial PSGL1, along with GPIb binding to von Willebrand factor, facilitate platelet adhesion to endothelial cells. These interactions not only contribute to thrombus formation but also support immune cell migration [14, 15].

Interactions with Immune Cells

In their inactive state, platelets have limited capacity to stimulate the immune system. Upon activation, however, they express adhesion molecules such as P-selectin, which binds to PSGL1 and sLeX in a FUT7-dependent manner. This interaction enables platelets to form aggregates with immune cells. Elevated levels of platelet-leukocyte aggregates, as well as increased platelet-derived extracellular vesicles and soluble P-selectin, are observed in autoimmune conditions such as SLE, rheumatoid arthritis, and antiphospholipid syndrome (APS). These findings suggest that activated platelets play a critical role in the formation of such aggregates and in disease progression [7, 16].

Main Mechanisms of platelet activation in immune-mediated inflammatory diseases:

Platelet activation occurs through multiple mechanisms in immune-mediated inflammatory conditions, involving specific receptors and stimuli that trigger their response [7]. These pathways include:

1. **Interaction with Immune Complexes:** Platelets bind to immune complexes through Fc receptors, such as FcγRIIA (targeting IgG), FcαRI (for IgA), and FcεR (for IgE), thereby amplifying inflammatory processes.
2. **Direct Autoantibody Stimulation:** Autoantibodies, including antiphospholipid and antiplatelet antibodies, can directly activate platelets without the need for receptor involvement.

3. **Toll-Like Receptor (TLR) Activation:** Microbial components, such as bacterial DNA and viral RNA, engage toll-like receptors on platelets (e.g., TLR4, TLR7, and TLR9), contributing to immune and inflammatory responses.
4. **Response to Non-Immunologic Triggers:** Platelets are also activated by non-immune factors, such as collagen (via GPVI), ischemia-reperfusion injury, reactive oxygen species, and nucleotide signaling through purine receptors (P2Y and P2X), which are stimulated by ADP and ATP, playing a role in diverse pathological conditions [16].

These mechanisms are fundamental to platelet involvement in immune responses, inflammatory diseases, and thrombosis. Platelet receptors involved in the pathogen recognition in different diseases is summarized in **Table 1**.

Table 1: Platelet receptors involved in pathogen recognition in different diseases [23-26]

Receptor	Pathogens/PAMPs
	PRRs
CLRs	
CLEC-2	HIV, DV, CpG ODN
DC-SIGN	HIV, DV
TLRs	
TLR2	Periodontopathogens, HCMV, Pam3CSK4
TLR4	LPS
TLR9	CpG ODN
NLRs	
NLRP3	DV-induced ROS products
NOD2	MDP
	Haemostatic Receptors
GPVI	HCV, SSL5, CpG ODN
GPIb	SSL5, SrpA, GspB, Hsa. Protein A (SpA), H. Pylori
Integrin αIIbβ3	Hantavirus, Adenovirus, SSL5, SdrG, PadA, IsdB, FnBPA, FnBPB, ClfA, ClfB
Integrin α2β1	Rotavirus
FcγRIIA	IgG-opsonized cells, IAV (H5N1), FnBPA, FnBPB
P2Y12	CpG ODN

Impact of Platelet-Immune Cell Interactions

A groundbreaking 2003 study demonstrated the significant role of platelets in modulating adaptive immune responses during viral infections. The infusion of platelets restored immune responses in vitro and in vivo, while platelet-depleted mice exhibited weaker immunity to adenovirus. This study highlighted the role of CD40L on platelets in activating CD8+ T cells via dendritic cell modulation and promoting B cell isotype switching under viral stress. Over the years, research has expanded our understanding of platelet interactions with both innate and adaptive immune cells [16].

Innate Immune Cell Interactions

Neutrophils, prominent in several immune-mediated inflammatory diseases (IMIDs) such as systemic lupus erythematosus (SLE), vasculitis, inflammatory bowel disease (IBD), and type 1 diabetes, contribute to tissue damage through immunogenic cell death. Elevated platelet-neutrophil aggregates in sickle cell disease patients decrease with platelet inhibitors or antibodies [17].

In immune thrombocytopenic purpura (ITP), active disease is associated with impaired regulatory T cell (Treg) function. Although platelet counts normalize with treatment, Treg function remains impaired, indicating a complex interaction. Modifications to P-selectin glycoprotein ligand-1 (PSGL1) with sialyl Lewis X (sLeX) motifs affect Treg and T follicular regulatory cell function, leading to changes in gene expression and reduced immunosuppressive activity. Dysregulated platelet activation significantly influences T cell behavior, but the mechanisms remain under investigation [16].

Role of Platelets in End-Organ Damage

Platelets engage with innate and adaptive immune cells to influence their function, driving inflammatory and autoimmune processes. These interactions, along

with the release of soluble factors, contribute to immune-mediated inflammatory diseases and organ damage [18].

Tissue Damage and Fibrosis

In multiple sclerosis, an autoimmune disorder affecting the brain, platelets infiltrate the central nervous system (CNS) before T cells, promoting immune-mediated damage through apoptosis and cytokine release. Kidney-targeted IMIDs, including SLE and systemic sclerosis, are associated with platelet aggregation and microthrombi formation in renal microcirculation. Platelets are also implicated in fibrosis across various organs, such as the heart, kidneys, lungs, and skin, through the release of TGFβ, which drives fibroblast growth, extracellular matrix breakdown, and upregulation of fibrotic genes. Other factors, such as thymic stromal lymphopoietin and serotonin, are linked to fibrosis in systemic sclerosis, though some evidence suggests platelets may also support macrophage reprogramming [21, 22].

Therapeutic Targeting of Platelets

Given their role in inflammation and tissue damage, targeting platelet activation and interactions with immune cells is a promising therapeutic strategy for IMIDs [17, 20].

Preventing Platelet Activation

Strategies include inhibiting agonist binding, cyclooxygenase (COX) activity, or specific ligand-receptor interactions such as P-selectin binding. While P2Y12 inhibitors are effective in cardiovascular diseases, they may worsen outcomes in severe COVID-19 cases by exacerbating the inflammatory response. Aspirin, a COX inhibitor, is used to prevent cardiovascular disease and platelet activation, though it is less effective in systemic lupus erythematosus (SLE) compared to P2Y12 inhibitors, particularly in reducing platelet-leukocyte aggregates and platelet surface markers like P-selectin and CD40L [17].

CONCLUSION:

This review highlights platelets' role in immune-mediated inflammatory disorders (IMIDs), focusing on their contribution to organ damage and disease progression. Key gaps include understanding platelet–immune cell interactions, their mechanisms, and their role in neutrophil migration to internal organs. Therapeutic strategies must balance reducing platelet-driven inflammation with minimizing bleeding risks by targeting specific pathways like adhesion and co-stimulatory molecules or inflammatory mediators. Research continues to reveal the significant role of platelets in immune responses, highlighting their influence in inflammation beyond their traditional function in blood clotting. Despite their small size and lack of a nucleus, platelets are pivotal in modulating inflammation through direct interactions with immune and non-immune cells or by releasing inflammatory mediators. Their abundance and ability to engage in complex mechanisms amplify their impact on inflammatory diseases. As our understanding of platelet-driven regulation in inflammation grows, it opens avenues for therapeutic strategies targeting platelet-mediated interactions, with the potential to mitigate disease progression in inflammatory and infectious conditions.

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